PATENT
Attorney Docket No. **HOGAN-04448**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Kirk Hogan	Group No.:	1655
Serial No.:	09/613,887	Examiner:	J.E. Goldberg
Filed:	July 11, 2000		
Entitled:	**Methods and Compositions for Perioperative Genomic Profiling**		

AMENDMENT AND RESPONSE TO OFFICE ACTION DATED APRIL 10, 2002

BOX NON FEE AMENDMENT
Assistant Commissioner for Patents
Washington, D.C. 20231

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Dated: July 8, 2002

By: Susan M. McClintock
Susan M. McClintock

Madam:

The following communication is responsive to the Office Action mailed April 10, 2002, due on or before July 10, 2002. The Applicant respectfully requests reconsideration of the Application in view of the following amendment and remarks.

A clean version of the rewritten, added, and or cancelled claims with instructions for entry pursuant to 37 C.F.R., Section 1.121(c)(1)(i) is included beginning on the next page of this communication. A marked up version of the rewritten, added, and/or cancelled claims pursuant to 37 C.F.R., Section 1.121(c)(1)(ii) is attached as Appendix I. A clean version of the entire set of pending claims pursuant to 37 C.F.R., Section 1.121(c)(3) as they should appear following entry of this amendment is attached as Appendix II.

I. IN THE CLAIMS

Please substitute the following claims for the previously pending claims.

21. A method of screening a patient perioperatively to determine a risk for complications during a surgical procedure associated with known genetic variations comprising:

a) obtaining a sample from a perioperative subject, said perioperative subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure; and

b) subjecting said sample to an assay for detecting two or more nucleic acid genetic markers to generate a genomic profile for use in selecting a perioperative course of action, wherein said subjecting step occurs after said patient is scheduled for surgery but before completion of said surgical procedure, thereby determining a risk for complications during said surgical procedure.

30. The method of Claim 21, wherein said two or more nucleic acid genetic markers comprise mutations in two or more genes, said genes selected from the group consisting of BChE, CYP2D6, MTHFR, MS, CBS, F 5 Leiden, Prothrombin, RYR1, CACNA1S, and CPT 2.

32. A method for selecting conditions for a surgical procedure by screening a patient perioperatively to determine a risk for complications during a surgical procedure associated with known genetic variations comprising:

a) obrtaining sample from a perioperative subject; and

b) subjecting said sample to an assay for detecting two or more nucleic acid genetic markers known to be associated with perioperative phenotypes to generate a genomic profile for use in selecting a surgical procedure treatment course of action; and

c) subjecting said subject to a surgical procedure, wherein conditions for said procedure are selected using said genomic profile.

36. The method of Claim 32, wherein said two or more nucleic acid genetic markers comprises a mutation in two or more genes, said genes selected from the group consisting of BChE, CYP2D6, MTHFR, MS, CBS, F 5 Leiden, Prothrombin, RYR1, CACNA1S, and CPT 2.

37. A method of screening a patient perioperatively to determine a risk for complications during a surgical procedure from known genetic variations comprising:

a) obtaining sample from a perioperative subject; and

b) subjecting said sample to an assay for detecting two or more nucleic acid genetic markers clinically associated with two or more conditions selected from the group consisting of butyrylcholinesterase deficiency, poor debrisoquine metabolism, thrombus, and malignant hyperthermia to generate a genomic profile, wherein said genomic profile provides information for use by a physician in determining a risk for complications during a surgical procedure.

REMARKS

Claims 1-20 were filed in the original case. Claims 1-20 were cancelled and claims 21-41 were added in a previous amendment. Therefore claims 21-41 are currently pending.

In the Office Action dated April 10, 2002, the Examiner has withdrawn rejections from the previous Office Action. However, the Examiner has added a number of new rejections. The currently pending rejections are:

1) Claims 21 and 32 stand rejected under 35 U.S.C. §102(b); and

2) Claims 21 - 41 stand rejected under 35 U.S.C. §103(a)

Each of these grounds of rejection is addressed in detail below.

I.) THE CLAIMS ARE NOT ANTICIPATED

The Examiner has rejected the claims as allegedly anticipated by several references. The Federal Circuit has stated the relevant analysis for anticipation as follows:

"A claim is anticipated only if each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference."[1]

Applicant respectfully submits that none of the references cited by the Examiner teach each element of the claims.

I. a. Posey *et al.* and Boral *et al.* Do Not Anticipate the Claims

Claims 21 and 32 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Posey *et al.* and by Boral *et al.* (hereinafter "Posey" and "Boral"). Applicant respectfully disagrees. Posey reviews the uses of blood and blood products, the hazards of blood transfusion, and precautions that can be taken to minimize risks to the patient. Boral teaches inventory control of blood products using a phenotypic test (the antibody type and screen), as a substitute for routine two-unit complete cross-match in elective surgical procedures rarely necessitating blood transfusion.

In order to further the prosecution of the present case, while not acquiescing to the Examiner's argument, and retaining the right to prosecute the original claims (or similar claims) in the future, Applicant has amended claims 21, 30, 32, 36, and 37 to recite "two or more nucleic acid genetic markers". The references cited by the examiner do not teach detection of nucleic acid genetic markers. In view of the above, Applicant respectfully requests that the rejection be withdrawn.

I. b. Bidwell *et al.* Does Not Anticipate the Claims

Claims 21 and 32 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Bidwell and Hui (hereinafter "Bidwell). Applicant respectfully disagrees. Bidwell teaches PCR-based HLA-DR and DQ allotyping before a kidney or bone marrow transplantation surgical procedure can be scheduled. Thus, on its face, Bidwell fails to anticipate an element of the instant claims i.e. "a patient scheduled for a surgical procedure". Although the Examiner's concession ("While the exact date for surgery may be dependent upon finding a suitable match,") is correct, the Examiner's ensuing contention (" . . . the patient was

[1] *Verdegall Bros. V. Union Oil of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)

scheduled for a surgical procedure as required by the instant claims.") is clearly erroneous. In the absence of a suitable transplantation match, no surgery is scheduled and no surgery takes place; the presence of a suitably matched donor is an absolute prerequisite to scheduling surgery. Only if a suitable match is identified, may surgery be scheduled. Only then could a perioperative genomic profile be generated. The perioperative interval is defined without ambiguity in the Specification (page 21) and claims, as extending from the point "when the patient is scheduled for surgery". To the contrary, Bidwell is directed to whether or not to schedule surgery in the first place. Data collected under Bidwell is for use before surgery is scheduled. Therefore Bidwell cannot anticipate the present claims.

The Applicant's claims expressly recite that once a surgical procedure is scheduled in fact, then genetic markers are used to generate a genomic profile which will improve the safety of the perioperative course itself. Claim 21 is specific, definite and unequivocal: "... wherein said subjecting step occurs after said patient is scheduled for surgery but before completion of said surgical procedure, thereby determining a risk for complications during said surgical procedure." Thus, Bidwell does not teach "a patient scheduled for a surgical procedures." Morevover, Bidwell does not teach "to generate a genomic profile". Nor does Bidwell teach "for use in selecting a perioperative course of action", for example, whether or not a patient scheduled for kidney or bone marrow transplantation is at increased risk for thrombosis, sepsis or malignant hyperthermia. Indeed, Bidwell does not teach genomic testing or use of genomic data of any kind within the perioperative interval. Contrary to Bidwell, the problem solved by the present invention is not to determine whether or not surgery should be done. Rather, it is to make inevitable surgery (i.e. surgery which has been scheduled) safer.

In view of the failure of Bidwell to teach all elements and limitations of claims, Applicant respectfully requests that the rejection be withdrawn.

II. THE CLAIMED INVENTION IS NON-OBVIOUS

The Examiner has rejected the claims as allegedly being obvious in view of a number of references. None of these references, alone or combination, teach or suggest generation of a genomic profile for use in selecting a perioperative course of action. None of these references, alone or in combination, teach or suggest generation of a genomic profiles for use

in selecting a surgical procedure treatment course of action. None of these references, alone, in combination, or (as the Examiner infers) in combinations of combinations, teach or suggest detecting two or more genetic markers clinically associated with two or more conditions.

Applicant asserts that the Examiner has not met the burden of establishing a *prima facie* case of obviousness. A *prima facie* case of obviousness requires the Examiner to cite to references that (a) disclose all the elements of the claimed invention, (b) suggest or motivate one of ordinary skill in the art to combine or modify those elements to yield the claimed combination, and (c) provide a reasonable expectation of success should the claimed combination be carried out.[2] Failure to establish any one of these three requirements precludes a finding of a *prima facie* case of obviousness and, without more, entitles Applicant to allowance of the claims at issue. The cited art fails to establish *prima facie* obviousness because there is no teaching, suggestion or motivation to make the Examiner's selections and combinations of the cited references (i.e. Miller + Quanne, Miller + La Du, Miller + Evans, Miller + Poort, etc.).

Furthermore, even if such selections and combinations were permissible (and they are not), the cited references do not teach or suggest every element of the presently claimed invention. The element "subjecting said sample to an assay for detecting two or more genetic markers clinically associated with two or more conditions . . ." is lacking in the combinations asserted by the Examiner. Only through impermissible hindsight in making combinations of combinations (i.e. [(Miller + Quanne) + (Miller + La Du) + (Miller + Evans) + (Miller + Poort) + etc.]) is the Examiner able to reconstruct an approximation of the present invention. As well, the cited art fails to establish *prima facie* obviousness because there is no teaching, suggestion or motivation in the prior are to make the Examiner's combinations of combinations. Moreover, even were the Examiner's reproduction permissible in hindsight (and it is not), the Examiner has failed to reconstruct the invention under the claims.

[2] See, e.g., *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990); and *In re Dow Chemical Co.*, F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

II. a. The Examiner's Combination of "Miller" with Prior Art References i.e. (Miller + Quanne), (Miller + LaDu), (Miller + Poort), etc. Fails to Establish a *Prima Facie* Case of Obviousness

In the office action dated 10/24/01 the Examiner rejected claims 21-28, 30-36 under 35 U.S.C. §103(a) (pages 6-12) as being non-patentable for obviousness over a number of references teaching genotype-phenotype associations, including Quanne *et al.*, Acta Anaesthesiologica Scandinavica ("hereinafter "AAS") and La Du, Pharmacogenetics and Evans, and Poort *et al.* In the 2/8/02 Amendment and Response, Applicant pointed out that the cited references fail to teach the element of testing in the perioperative period. These rejections were subsequently withdrawn in the Office Action of 4/10/02. To remedy the defect of the missing element required to establish *prima facie* obviousness under 35 U.S.C. §103(a) (i.e. Claim 21: "a sample from a perioperative subject", "use in selecting a perioperative course of action," Claim 32: "genetic markers associated with perioperative phenotypes") the Examiner now cites "Miller" in combination, pair by pair, with each or the cited references of the earlier 10/24/01 Office Action.

As designated by the Examiner, "Miller" is a chapter authored by G.A. Gregory appearing in the textbook Anesthesia, vol. 2, pages 1323-1333, edited by R.A. Miller, in 1981. Miller discusses routine anesthesia for out-patients, including pre-operative phenotypic testing of hemoglobin level, urinalysis, serum electrolytes, and electrocardiogram. The Examiner concedes "Miller does not specifically teach analyzing the blood taken from the patient within two days prior to surgery for "known genetic variations"." Nor does Miller teach "to generate a genomic profile for use in selecting a perioperative course of action". Indeed, there is no teaching in Miller to perform genetic testing of any kind.

The Examiner concedes that there is no single prior art reference teaching all of the elements and limitations of the present claims. Also, there is no teaching or motivation in Miller to select and combine with each of the references cited in the earlier 10/24/01 Office Action. In addition, there is no teaching or motivation in the references cited in the earlier 10/24/01 Office Action to combine with Miller. Moreover, there is no teaching elsewhere motivating the combination of Miller with each of the Examiner's selections cited in the earlier 10/24/01 Office Action. Nevertheless, the Examiner asserts that the combination of

Miller with each of the references cited in the earlier 10/24/01 Office Action is sufficient to prove the motivation of an artisan of ordinary skill in the art. To the contrary, in asserting these *post hoc* selections and combinations (i.e. selections and combinations only possible to one in possession of the present disclosure) as *prima facie* evidence of obviousness, the Examiner employs an incorrect standard of obviousness. As well, the Examiner fails to meet the correct legal standard in providing evidence of the motivation to select and combine cited prior art references. Moreover, the Examiner ignores clear-cut, objective evidence of non-obviousness put forth by the Applicant.

II. a. 1. Substantial Utility is an Incorrect Standard of Obviousness

For each of the paired combinations of Miller with references cited in the earlier 10/24/01 Office Action, the Examiner argues in the 4/10/02 Office Action that the claims of the present disclosure would have been rendered obvious to one of ordinary skill in the art at the time the invention was made because of the manifest utility of the invention:

Miller + Quanne (4/10/02 Office Action pages 6-7):

"Quanne teaches that the mutation reported satisfies the genetic criteria necessary for demonstration of a causal mutation and as such this mutation should be of significant value for MHS diagnosis by genetic means (page 474, col. 1.). Quanne analyzes genomic DNA from peripheral blood for the presence of the mutations (page 474, col 2.)

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have sampled patients prior to subjecting the patient to anesthetics, as taught by Miller, to determine whether they were at risk of MH, as taught by Quanne."

Miller + "AAS" + La Du (4/10/02 Office Action pages 12-13):

"La Du et al (herein referred to as La Du) teaches butyrylcholinesterase variants which have been found in individuals who have responded abnormally to the muscle relaxant succinylcholine. Variants with increase activity are resistant to succinylcholine and may require two or three doses to achieve the desired state of paralysis (page 80).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have sampled patients within two days prior to surgery, as

taught by Miller, to subjecting the patient to succinylcholine, for example, to determine whether they were resistant to the drug, as taught by AAS and La Du."

Miller + "Pharmacogenetics" + Evans (4/10/02 Office Action pages 15-16)

"Evans teaches that "many opioid analgesics are activated by CYP2D6 rendering 2-10% of the population who are homozygous for nonfunctional CYP2D6 mutant alleles relatively resistant to opioid analgesic effects. Thus is it not surprising that there is remarkable interindividual variability in the adequacy of pain relief when uniform doses of codeine are widely described" (page 489, col. 1). Evans teaches that individualizing drug doses can improve clinical outcome (page 491, col. 1).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have sampled patients within two days prior to surgery, as taught by Miller, to subjecting the patient to anesthetics to determine whether they were at risk of being a poor metabolizer of a drug, namely codeine."

Miller + Poort (4/10/02 Office Action page 17)

"It is well known in the art that venous thromboembolism can occur without apparent cause, after surgical procedures or trauma. Poort also teaches that factor V Leiden is the most common hereditary risk factor for thrombosis. Poort teaches two genetic markers which are associated with thrombosis.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have sampled patients prior to subjecting the patient to anesthetics, as taught by Miller, to determine whether they were at risk of thrombosis, as taught by Poort."

For each of the paired combinations of Miller with the references cited in the earlier 10/24/01 Office Action, the Examiner acknowledges the significant utility of the present claims over the references, then argues that "Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art . . . " to select and test for the genetic marker in question. In accord with the Examiner, the Applicant respectfully stipulates the substantial usefulness of the present invention. However, contrary to the Examiner's arguments, substantial utility does not void non-obviousness, nor does obviousness follow from substantial utility. Congress mandates that the U.S.P.T.O. and C.A.F.C. analyze utility and

obviousness under independent evidentiary standards, i.e. 35 U.S.C. §101 vs. 35 U.S.C. §103(a), respectively. Hence, inventions with *de minimis* utility may be either obvious or non-obvious. Or, as with the present disclosure, inventions with substantial utility may be non-obvious as a matter of both fact and law. Thus, while the 4/10/02 Office action documents the Examiner's recognition of the substantial utility of the present Claims, the Examiner's arguments fail to analyze non-obviousness by the correct legal standard. Indeed, considering the benefit of the present invention, the failure of the prior art to teach the claimed methods is objective evidence of non-obviousness.

II. a. 2. The Examiner's Combinations of Miller with Prior Art References Fail to Establish a *Prima Facie* Case of Obviousness by the Correct Legal Standard

An essential requirement for a *prima facie* case of obviousness is whether a person skilled in the art would be motivated to modify the reference to arrive at the claimed invention.[3] The requirement that the Examiner make a showing of a suggestion, teaching or motivation to combine the prior art references is an essential evidentiary component of an obviousness holding. The factual inquiry whether to combine references "must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with."[4] The law requires that evidence of a suggestion, teaching, or motivation to combine prior art references "must be clear and particular".[5] "Broad conclusory statements regarding the teaching of multiple references, standing alone, are not evidence."[6]

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[3] *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988); *In re Jones*, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992)

[4] *In re Sang Su Lee* 277 F.3d 1338, 61 USPQ2d 1430 (Fed. Cir. 2002). See also, *Brown & Williamson Tobacco corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000) ("a showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential evidentiary component of an obviousness holding'") (quoting *C.R. Bar, Inc. v. M3 Sys. Inc.*, 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998)); *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references.")

[5] *In re Dembiczak*, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999), *citing C.R. Bard*, 157 F.3d 1340 at 1352, 48 USPQ2d at 1232.

[6] *In re Dembiczak*, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999), citing *McElmurry v. Arkansas Power & Light Co.*, 995 F.2d 1576, 1578, 27 USPQ2d 1129,1131 (Fed. Cir. 1993).

To the contrary, each of the Examiner's statements regarding the ordinary artisan's motivation to select and combine references are conclusory and unsupported. The Examiner has provided no support in the form of prior art reference, affidavit, declaration, or concrete evidence other than in the form of an argument, teaching that the artisan of ordinary skill would have been motivated to select and combine all, some or even one of the previously cited references with Miller as the Examiner speculates. This is because the only source guiding the Examiner to pair Miller in combination with each of the references cited in the earlier 10/24/01 Office Action is the present invention, i.e. through the hindsight of one in possession of the present disclosure.

II. a. 3. Objective Evidence of Non-Obviousness

In the Office Action dated 4/10/02 the Examiner has made multiple assertions of what an ordinary artisan would have "clearly recognized" regarding "the benefit" (i.e. utility, see section II. a. 1. above) of testing under the Claims of the invention at the time the invention was made:

Miller + Quanne (4/10/02 Office Action page 7.):

"The ordinary artisan would have clearly recognized the benefit of testing an individual prior to surgery and subjection to the anesthesia for known genetic markers associated with a condition which was triggered by anesthetics."

Miller + "AAS" + La Du (4/10/02 Office Action page 13.)

"The ordinary artisan would have clearly recognized the benefit of testing an individual within two days prior to surgery and subjection to succinylcholine for known genetic markers associated with a condition which causes certain individuals to have a dramatic degree of resistance to the drug because they destroy it so rapidly requiring two or three doses to achieve the desired state of paralysis."

Miller + Pharmacogenetics + Evans (4/1/02 Office Action page 16.)

"The ordinary artisan would have clearly recognized the benefit of testing an individual within two days prior to surgery and subjection to codeine for known genetic markers associated with a condition which causes certain individuals to be poor metabolizers."

In addition to impermissibly confusing utility with obviousness (see II. a. 1. above), each such speculation on the part of the Examiner concerning what would have been "clearly recognized" by an artisan of ordinary skill at the time the invention was made is conclusory and unsupported. The Examiner is unable to provide support in the form of a prior art reference, affidavit, declaration or any other concrete evidence for all, some or even one of the Examiner's assumptions about an what one of ordinary skill in the art would have "clearly recognized".

Moreover, countering the Examiner's assertions, the Applicant provides ample objective evidence that an artisan of ordinary skill would not, and does not, recognize the benefits of the present invention. Thus, in the Declaration of Kirk Hogan M.D. dated 2/7/02, a review of the grant Application "Perioperative Genomic Profiles" by the Grant Committee of the Anesthesia Patient Safety Foundation describes the disclosed invention as "without clear clinical value". This statement by those skilled in the art stands starkly opposite the Examiner's unsupported proclamation that the benefits of the claims "would have been clearly recognized." Moreover, in language directly on point sustaining a finding of non-obviousness, the Grant Committee declares ". . . this study seems to be going in the *opposite direction*. . . . The direction of anesthetic evaluation is presently *to not routinely do any preoperative studies*."

The Examiner, responding in the 4/10/02 Office Action to this objective evidence of non-obviousness, confuses the fact of non-obviousness ("It would take the issue of patient safety in a new direction."), with the reasons for non-obviousness i.e. cost, confidentiality, ethics. (Applicant notes that these are only some of the reasons.) The reasons for non-obviousness are immaterial to a finding of non-obviousness in fact. The APSF grant review furnishes uncontradicted, objective, and factual evidence that, contrary to the Examiner's conclusory and unsupported statements, the ordinary artisan would not have clearly recognized the benefit of testing an individual before surgery to generate perioperative genomic profile.

The Applicant's 2/8/02 Amendment and Response also provides references Gregory and Kirby teaching the fact that in contemporary practice routine perioperative testing of any kind is to be avoided. In the Office Action of 4/10/02 the Examiner responds that "the cited art provides suggestion that with regard to RYR1, BchE, prothrombin, etc. genes, testing prior

to surgery would be certainly advantageous since mortality and complications may be avoided." Again, the Examiner impermissibly confuses utility ("certainly advantageous") with obviousness. And again, the Examiner's response is conclusory and unsupported by fact. In the following sentence the Examiner asserts "While it is clear that many in the medical field do not believe that routine genetic testing provides sufficient valuable information to warrant its cost, this does not imply that the art has not conceived of or thought about perioperative genetic testing." The Examiner is doubly in error. First, far from being "clear", the Examiner has provided no evidence that anyone in the medical field has considered perioperative genomic profiles regardless of cost or other factors. Second, the Examiner has provided no factual evidence that the art has in fact conceived of or "thought about" perioperative genomic profiles prior to the present disclosure. In fact, Hopkins (cited in the 2/8/02 Amendment and Response), the single reference that mentions DNA-based testing for one trait relevant to the disclosure (malignant hyperthermi) *teaches away* from perioperative genomic profiling, in stating "DNA-based testing is precluded at present" (i.e. 2000) (page 125.).

As explained in references cited in the Amendment and Response of 2/8/02, and the 2/7/02 Declaration of Kirk Hogan M.D., and uncontradicted in the Examiner's assertions, the ordinary artisan would not have clearly recognized the benefit of testing an individual for genetic markers prior to surgery in order to generate a perioperative genomic profile. Applicant submits herewith the Second Declaration of Kirk Hogan, M.D. The Declaration explains that, even today in July, 2002 (let alone at the filing date of the present invention), the state of the art in medical practice is not to test subjects for multiple genetic markers in the perioperative period. Dr. Hogan explains facts that show, in view of the state of the art, one skilled in the art would not, upon reading the prior art references cited by the Examiner, recognize a benefit of testing individuals in the perioperative period, and would not have been motivated to test these individuals in the perioperative period for the expected benefit of determining whether the patient possessed any mutations which were linked to known conditions. For example, in the "Practice Advisory for Preanesthesia Evaluation: A Report by the American Society of Anesthesiologists Task Force on Preanesthesia Evaluation", 2002 (attached) no perioperative genetic testing of any kind is advocated, discussed or mentioned even today. The Advisory is based on a review of all relevant studies including expert and

public consensus (i.e. ordinary artisans) opinion aimed at creating a consensus-based assessment of the currently available scientific literature and opinion addressing the issue of preoperative evaluation. In the complete accompanying bibliography (attached) references are appraised addressing many of the phentoypes contemplated by the present invention, including thrombosis, butyrylcholinesterase deficiency and malignant hyperthermia. However, in support of a finding of the non-obviousness of perioperative genomic profiles, no genotypes are considered for preanesthesia evaluation in the Practice Advisory.

The relevance of the Task Force's Advisory to the analysis of non-obviousness of the present invention is twofold. First, the Advisory concludes: "*Routine preoperative tests* (*i.e.* tests intended to discover a disease or disorder in an asymptomatic patient) do not make an important contribution to the process of perioperative assessment and management of the patient by the anesthesiologist." This statement is expressly antithetical to the Examiner's assertion that "an ordinary artisan would have been motivated to test these individuals prior to surgery for the expected benefit of determining whether the patient possessed any mutations which were linked to the known condition . . .".

Second, the Task Force on Preanesthesia Evaluation's Practice Advisory directly negatives the Examiner's speculation over what the ordinary artisan "would have clearly recognized". In appraising all of the world's literature deemed relevant by those skilled in the art, and incorporating both expert and survey opinion (i.e. from anesthesiologists of ordinary skill in the art, members of the American Society of Anesthesiologists, and open forums), the Practice Advisory expressly establishes what would have been obvious to an artisan or ordinary skill. Tellingly, genetic testing and perioperative genomic profiling are not found in the reference. Hence, the Examiner's allegations regarding what would have been "clearly recognized" by an ordinary artisan are in plain error under the claims of the present invention and factual evidence supplied by the Applicant.

If, as the Examiner contends, perioperative genomic profiling would have been clearly obvious to the ordinary artisan, then the Examiner would be able to cite a published reference, a change in practice, or other objective evidence in support, but there is none. Perioperative genomic profiling has not and is not being done. Perioperative genomic profiling has not been and is not advocated. The Examiner is unable to put forward evidence indicating that the ordinary artisan would have "clearly recognized" or "would have been motivated to test" in

the generation of perioperative genomic profiles at the time the invention was made, absent the present invention now in the Examiner's possession.

II. b. The Examiner's Combination of Combinations i.e. [(Miller + Quanne) + (Miller + AAS + LaDu) + (Miller + Pharmacogentics + Evans) + (Miller + Poort)] to Reconstruct the Present Invention Fails to Establish a *Prima Facie* Case of Obviousness

On page 18 of the 4/10/02 Office Action the Examiner impermissibly reconstructs the present invention as follows:

"Claims 29-30, 36-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Quanne et al (Human Molecular Genetics, Vol 3, No. 3, page 471-476, 1994) as applied to Claims 21-28, 31-35 above; Miller (Anesthesia, Vol. 2, pages 1323-1333) Miller (Anesthesia, Vol.2, pages 1323-1333, 1981) in view of Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991) as applied to Claims 21, 26-28, 31-34 above; Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) and Evans et al (Science, Vol 286, pages 487-491, October 1999) as applied to Claims 21, 26-28, 31-34 above; and Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Poort et al (Blood, Vol 88, No 10, page 3698-3703, 1996) as applied to Claims 21, 28, 30-32, 36 above."

The Examiner's impermissible reconstruction of the invention through retrospective selection and combination of prior art references guided by the disclosure fails to establish a *prima facie* case of obviousness for four reasons. First, the Examiner fails to cite a reference which discloses all elements of the claims. Second, the Examiner's confusion of substantial utility with obviousness employs an inappropriate standard. Third, the Examiner is unable to provide a teaching which motivates the Examiner's combination of combined prior art references. There is no teaching in support of the Examiner's conclusory assertions regarding first order combinations (i.e. Miller pair by pair with the prior art references cited in the 10/24/01 Office Action), combined into second order combinations to arrive at the invention.

Fourth, even if such combinations of combinations of combinations were permissible (and they are not) the invention would be non-obvious.

II. b. 1. The Examiner's Reconstruction of the Invention through Combinations of Prior Art Combinations to Establish a *Prima Facie* Case of Obviousness is Defective

A *prima facie* case of obviousness requires the Examiner to cite to a reference which discloses all the elements of the claimed invention.[2] Failure to establish this requirement precludes a finding of a *prima facie* case, and without more, entitles the Applicant to allowance of the claims in issue. Claim 37 teaches "subjecting said sample to an assay for detecting two or more genetic markers clinically associated with two or more conditions". With respect to the combination of the various (Miller + Quanne), (Miller + AAS + La Du), (Miller + etc.) combinations, thereby arriving at the present invention, the Examiner concedes:

> "None of the cited references specifically discuss testing multiple known markers which are associated with different conditions, i.e. known genetic markers into a single assay for determining whether individuals are at risk during surgical procedures." (Office Action, page 19)

Nor do any of the cited references impliedly discuss testing multiple known markers. Moreover, none of the cited references, either singly or in paired combinations, teach assembly of higher order combinations. That is, none of the references teach the Examiner's combinations of combinations.

II. b. 2. Substantial Utility of Combinations of Prior Art Combinations is an Incorrect Standard of Obviousness

In rejecting Claims 29-30, 36-41 under 35 U.S.C. §103(a) the Examiner's argument concludes (Office Action 4/10/02 page 20.): "The benefit of screening individuals for several of these prevalent mutations which are related to surgery would have allowed the anesthesiologist to determine whether plausible substitutes may be provided to patients which would not cause these conditions to arise. . . . Combining more than one screening method to

determine the genomic profile of a patient would have provided the anesthesiologist with a more complete picture of the patient's genetic make-up." In these assertions the Examiner is merely reciting the uncontested utility of the present invention. However, these observations have no bearing on the *prima facie* case of obviousness. The Applicant does not dispute the Examiner's perceived utility of the Claims. However, the Applicant asserts that a utility standard in proxy for a *prima facie* finding of obviousness is impermissible.

The Examiner also contends: "It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the vast number of teachings, as exemplified by the extremely voluminous Information Disclosure Statement filed, to screen individuals prior to surgery for several genetic markers which are indicative of any number of conditions which are caused by anesthesia or are a result of anesthesia." The breadth and scope of the IDS reflects the absence of prior 103(a) art. In turn, the Examiner's statement is conclusory, unsupported by fact, and impermissibly confuses substantial usefulness of the disclosure with obviousness, objective evidence to the contrary.

II. b. 3. The Examiner's Reconstruction of the Invention through Combinations of Prior Art Combinations Fails to Establish a *Prima Facie* Case of Obviousness by the Correct Legal Standard

An essential requirement for a *prima facie* case of obviousness is whether a person skilled in the art would be motivated to modify the reference to arrive at the claimed invention.[3] The C.A.F.C. holds:

> The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification. . . . It is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious. This court has previously stated that "one cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.[7]

[3] *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988); *In re Jones*, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992)

[7] *In re Fritch*, 972 F.2d 1260, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992) (quoting *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988)).

Individual references cannot be "employed as a mosaic to recreate a facsimile of the claimed invention."[8] As well, "The invention must be viewed not with the blueprint drawn by the inventor."[9] Thus, absent a suggestion, teaching or motivation in the prior art to reconstruct the invention through selection and combination of prior art combinations, the Examiner has failed to establish a *prima facie* case of obviousness.

To the contrary, each of the Examiner's statements regarding the ordinary artisan's motivation to combine combinations of prior art references are conclusory and unsupported. The Examiner has provided no support in the form of prior art reference, affidavit, declaration, or concrete evidence other than in the form of an argument, teaching that the artisan of ordinary skill would have been motivated to combine the prior art combinations as the Examiner speculates. This is because the only source teaching the Examiner to reconstruct the invention through a combination of prior art combinations (i.e. the pairs of Miller in combination with each of the references cited in the earlier 10/24/01 Office Action) is the present invention. That is, through the selective hindsight of one in possession of the present disclosure.

The number of references cited by the Examiner, when combined with Miller, do not add weight to the failed *prima facie* case of obviousness because all suffer from identical defects: None teaches two or more genetic markers; None teaches two or more conditions; None teaches a combination of combinations; There is no published evidence teaching, suggesting or motivating the combination of prior art combinations. Thus, to reconstruct the present invention the Examiner must first argue that it would have been obvious to an artisan of ordinary skill to combine Miller with each of the prior art references cited in the 10/24/01 Office Action. Then, the Examiner must argue that it would have been obvious to the ordinary artisan to combine these combinations into an approximation of the present invention. But, the Examiner has provided no factual or legal support for the obviousness of either level of combination. Nor has the Examiner provided evidence that the claims would have been obvious to one not in possession of the invention.

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[8] *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1551, 220 USPQ 303, 312 (Fed. Cir. 1983), cert.denied, 469 U.S. 851, 105 S. Ct. 172, 83 L. Ed. 2d 107 (1984).

[9] *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985)

II. b. 4. Even if Reconstruction of the Invention through a Combination of Prior Art Combinations were Permissible (and it is not), the Invention is Non-Obvious

Despite the Examiner's elaborate hindsight reconstruction of the present invention detailed on page 18 of the 4/10/02 Office Action and quoted on page 15 above, the Examiner's reconstruction still fails to render the invention obvious under the claims. Specifically, the elements "for use in selecting a perioperative course of action", "for use in selecting a surgical treatment course of action" and "for use by a physician in determining a risk for complications during a surgical procedure" by, for example, selection of alleles according to express categories and criteria (e.g., Specification, pages 26-30) are lacking in the Examiner's cited prior art combinations, combinations of prior art combinations, or other references proffered by the Examiner. The Examiner can point to no evidence that these elements of the Claims would have been obvious to an artisan of ordinary skill at the time the application was filed.

Therefore, the Examiner has assembled an argument for rejection on the basis of obviousness by coupling assertions of the invention's clear-cut and undisputed utility, with incorrect, unsupported and conclusory guesses about what an ordinary artisan "would have clearly recognized" or "would have been motivated to do". In the first instance, substantial utility does not negative non-obviousness. In the second, the Examiner's guesses do not satisfy requirements for establishing the *prima facie* case of obviousness. Indeed the only source available teaching the Examiner to make these assertions are the present claims. In turn, objective, specific and ample evidence negating obviousness has been put forward by the Applicant, and has not been contradicted by the Examiner. For these reasons Applicant therefore respectfully requests that the rejection be withdrawn.

CONCLUSION

All grounds of rejection of the Office Action of April 10, 2002 have been addressed and reconsideration of the application is respectfully requested. It is respectfully submitted that the Applicant's Claims as amended should be passed into allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application Applicant encourages the Examiner to call the undersigned collect at (608) 218-6900.

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